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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,454	SINGH, SARMAN	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2-8 and 11-17* is/are allowed.

6)☒ Claim(s) *1, 9, 10 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/27/2010 has been entered. Claims 10-18 have been added. Claims 1-18 are pending.

New Ground(s) of Rejections

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 9, 10 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salotra et al (20030162182, August 28, 2003, filing date February 2002) in view of Reed et al (WO 9416331, July 1994) in view of Lowe et al () and Buck (Biotechniques, vol. 27, pages 528-536, 1999) and further in view of Belli et al (Am. J. Trop. Med. Hyg. Vol. 58, no. 1, pages 102-109, 1998).

Regarding claims 1, 9, 10 and 18, Salotra teach a primers and a kit for amplification and detection of kinesin related gene of Leishmania species in a sample, the method comprising the steps of (a) isolating DNA from a sample; (b) amplifying a target region from the DNA of step (a) using isolated primer sequences and heat stable DNA polymerase to obtain amplified fragments, (c) separating the amplified fragments of step (b); and (d) analyzing the fragment of step (c) to detect and characterize Leishmania species based on a banding pattern of the amplified fragments following electrophoresis (0025-0031 and 0038, see also Table 1 which gives results of PCR assay in KA and PKDL clinical samples and controls; see also 0034 which teaches the concept of a kit comprising reagents for performing the method. It is noted that the presence of an instruction manual is deemed inherent in the kit. Further MPEP states, "Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, >367 F.3d 1336,1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004))".

Salotra et al differs from the instant invention in that the reference does not teach the primer sequences consisting essentially of the sequences of SEQ ID NOS: 1-4 or wherein the primers are all used in a single polymerase chain reaction. However methods of isolating and designing sequences from a larger gene sequence is well known in the art. For example, Reed et al teach a nucleic acid sequence of Leishmania comprising a sequence substantially identical to the sequence of *SEQ ID NO: 1* (see page 17, SEQ ID NO: 2 which teaches a sequence 100% identical to SEQ ID NO: 1 at nucleotide position 2681 to 2697) (see alignment below);

```
SEQ ID NO: 1          1 CTAGAGCAGCAGCTTCG 17
                        |||||||||||||||||
Reed et al         2681 CTAGAGCAGCAGCTTCG 2697
SEQ ID NO: 2
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SEQ ID NO: 2 (see page 17, SEQ ID NO: 2 which teaches a sequence 100% identical to the sequence of SEQ ID NO: 2 at nucleotide position 2564 to 2580) (see alignment below);

```
SEQ ID NO: 2          1 CTTGAGCAGCAGCTTCG 17
                        |||||||||||||||||
Reed et al         2564 CTTGAGCAGCAGCTTCG 2580
SEQ ID NO: 2
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SEQ ID NO: 3 (see page 17, SEQ ID NO: 2 which teaches a complement sequence that is 100% identical to the sequence of SEQ ID NO: 3 at nucleotide positions 2797 to 2781) (see alignment below);

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SEQ ID NO: 3          1 CGTGGCCCTCGTGTTCT 17
                        |||||||||||||||||
Reed et al         2797 CGTGGCCCTCGTGTTCT 2781
SEQ ID NO: 2
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and SEQ ID NO: 4 (see page 17, SEQ ID NO: 2 which teaches a complement sequence 82. 4% identical to the sequence of SEQ ID NO: 4 at nucleotide positions 3265 to 3252) (see alignment below).

```
SEQ ID NO: 4          1 CGCGGCCCTCGTGT 14
                        ||||||||||||||
Reed et al         3265 CGCGGCCCTCGTGT 3252
SEQ ID NO: 2
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Lowe et al teach a method for designing primers and evaluating their performance wherein Lowe et al disclose a computer program for rapid selection of oligonucleotide primers for polymerase chain reaction (see page 1757, col. 1, abstract). Lowe et al. teach that all primers designed for over 10 gene products were experimentally tested and the results showed that all the amplification products specified by the primers are of the predicted size and also hybridize with the appropriate cDNA or internal oligonucleotide probe (see page 1760, col. 2, paragraph 1).

With regards to the issue of reasonable expectation of success in using such equivalents, Buck et al expressly provides a general teaching of evidence of the equivalence of primers. Specifically, Buck invited primer submission from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue; thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (see page 530, col. 1). When Buck tested each of the primers selected by the method of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Buck expressly states "The results of the

empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, col. 2)."

Therefore, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made, to combine the known nucleic acid sequence as taught by Reed with a step of generating primers and designing primers as taught by Lowe et al. to amplify and to detect kinesin related genes of Leishmania species as suggested by Salotra et al. Likewise, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95-control primers functioned, which represent 1/3 of all possible primers in the target region. Thus, the ordinary artisan could predictably expect a reasonable expectation of success that such primers generated using known sequences as taught by Reed and Salotra et al. in view of Lowe et al. and Buck et al would amplify or detection Leishmania species because the claimed primers are functional equivalents of the sequences taught by Salotra et al and further because Lowe et al. explicitly teaches that all primers designed for over 10 gene products were experimentally tested and the results showed that all the amplification products specified by the primers are of the predicted size (see page 1760, col. 2, paragraph 1).

The ordinary artisan would have been motivated to generate a number of said primers for detecting Leishmania species and place them in the form of a kit. Such selections of primers are considered functionally equivalent to the claimed primers of the instant invention. Selection of specific oligonucleotides for specific Tm represents

routine optimization with regard to sequence, length and composition of the oligonucleotide, which routine optimization parameters are explicitly recognized in Lowe et al. (This clearly shows that every primer would have a reasonable expectation of success). As noted in *In re Aller*, 105 USPQ 233 at 235, more particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. Routine optimization is not considered inventive and no evidence has been presented that the primer selection of Salotra was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Salotra et al in view of Reed et al do not expressly teach wherein multiple primers are used in the same PCR assay. However, the concept of using multiple primers in a multiplex PCR based assay is well known in the art.

For example, Belli et al teach a multiplex PCR reaction using multiple primers that allows simultaneous detection of the Leishmania genus (abstract and page 103, section entitled "Polymerase chain reaction amplification"). Belli et al teach that the multiplex reaction minimizes the number of PCRs necessary to characterize the Leishmania strains (see page 4, col. 2, last paragraph). Belli et al teaches that PCR offers certain advantages over classic techniques for diagnosis and characterization of infectious pathogens. Belli et al teach when appropriately applied, the PCR can be more specific, sensitive, versatile, and rapid than conventional methods; in addition, genetic information can be obtained in the process (last paragraph, col. 2, page 106).

Belli et al teaches that PCR is particularly useful in case of leishmaniasis, due to the requirement for parasitologic confirmation and to the limitations of classic methodologies (page 107, col. 1, second paragraph).

Therefore, it would additionally have been *prima facie* obvious for one of ordinary skill in the art at the time of the claimed invention to have been motivated to have modified the amplification reaction of Salotra et al in view of Reed et al and Lowe et al. and Buck et al to encompass a PCR reaction comprising the use of multiple primers in a multiplex reaction as taught by Belli et al. One of ordinary skill in the art at the time of the claimed invention would have been motivated to do for the advantages of reducing the number of PCRs necessary to characterize Leishmania strains and to increase specificity, sensitivity and versatility of detection as taught by Belli.

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Response to Arguments

6. Applicant traverses the rejection on the following grounds: Applicant states that Salotra does not teach using two sets of primers, nor does it teach the primers recited in the claims 1-4. Applicant states that Read does not provide a reason to select SEQ ID NOS: 1-4 or any other partial sequence. Applicant states that Lowe does not suggest that any of the rules provide two sets of primers that will provide unique band separation pattern for VL and PKDL causing strains of *Leishmania donovani*.

7. All of the arguments have been thoroughly reviewed and considered but is not found persuasive for the reasons that follow: While the examiner acknowledges

Applicant's arguments, it is noted that the selection and designs of primer sequences for detecting a specific target is well known in the prior art, when the gene from which the primers have been isolated is known. Applicant is again reminded that the prior art of Salotra et al and Reed et al had already taught the ordinary artisan to target the minicircle region conserved in all strains of Leishmania to detect different strains of Leishmania (see Belli, page 103; see Salotra et al which teaches primer designed for use in the method based on the donovani kinetoplast mini-circle sequence (see page 850, col. 2, section entitled "oligonucleotide primers"). Likewise, methods for aligning known nucleic acid sequences to arrive at primer and probe combinations are well-known and commonly applied in the prior art as taught by the cited references. For example, Salotra and especially Lowe et al and Buck et al provide evidence of selecting and/or designing primers from a larger known sequence. Buck et al provides evidence of the equivalence of primers in extension type assay, which include PCR. Thus, contrary to Applicant's arguments in this case, it is not unpredictable to design the primers and probes as claimed in the instant invention because the cited prior art has already given the ordinary artisan the necessary tools to design primer and probe to target gene sequences from Leishmania.

In response to Applicant's arguments concerning the advantages of the instant invention, it is noted that Applicant's arguments are not commensurate in scope with the claims as currently written. Applicant is reminded that the claims are not drawn to a method comprising specific method steps, but a product comprising oligonucleotides and reagents for kit. MPEP states "the fact that applicant has recognized another

advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious." See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In this case, this is particularly true because the prior art provides sufficient evidence that it would be obvious to select a combination of primers and place them in a kit for use in PCR type reactions.

Conclusion

8. Claims 1, 9, 10 and 18 are rejected. Claims 2-8 and 11-17 have not been rejected under prior art and contain allowable subject matter because while the prior art teaches sequences substantially identical to the sequences of SEQ ID NOS: 1-4 (see Reed et al and citation above), the art does not teach wherein said sequences are effective for detecting and differentiating VL and PKDL causing strains of Leishmania donovani as required by the claimed method. The combination of method steps recited in the claims 2-8 and 11-17 are the basis of allowability of those claims because the prior art does not provide any support for the use of the oligonucleotide sequences in the combination of method steps.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/

Examiner, Art Unit 1637